Dose-Related Behavioral, Subjective, Endocrine, and Psychophysiological Effects of the κ Opioid Agonist Salvinorin A in Humans

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Background: Salvia divinorum (Salvia) is an increasingly popular recreational drug amongst adolescents and young adults. Its primary active ingredient, Salvinorin A (SA)—a highly selective agonist at the κ opiate receptor—is believed to be one of the most potent naturally occurring hallucinogens. However, there is little experimental data on the effects of SA in humans.

Methods: In a 3-day, double-blind, randomized, crossover, counterbalanced study, the behavioral, subjective, cognitive, psychophysiological, and endocrine effects of 0 mg, 8 mg, and 12 mg of inhaled SA were characterized in 10 healthy individuals who had previously used Salvia.

Results: SA produced psychotomimetic effects and perceptual alterations, including dissociative and somaesthetic effects, increased plasma cortisol and prolactin, and reduced resting electroencephalogram spectral power. The SA administration was associated with a rapid increase of its levels in the blood. SA did not produce euphoria, cognitive deficits, or changes in vital signs. The effects were transient and not dose-related. SA administration was very well-tolerated without acute or delayed adverse effects.

Conclusions: SA produced a wide range of transient effects in healthy subjects. The perceptual altering effects and lack of euphoric effects would explain its intermittent use pattern. Such a profile would also suggest a low addictive potential similar to other hallucinogens and consistent with κ opiate receptor agonism. Further work is warranted to carefully characterize a full spectrum of its effects in humans, to elucidate the underlying mechanisms involved, and to explore the basis for individual variability in its effects.

Salvia divinorum (Salvia) is an increasingly popular recreational drug among adolescents and young adults. Salvia, a member of the mint family, has been used for centuries in traditional Mexican religious and medicinal rituals (1,2). Chewing or smoking Salvia leaves produces depersonalization and auditory and visual hallucinations. Salvinorin A (SA), the primary psychoactive component of Salvia is a potent and highly selective agonist at κ opiate receptors (KOR) (3). SA has no activity at other receptor systems—including dopaminergic, serotonergic, or N-methyl-D-aspartate (NMDA) receptors—that are involved in the mechanism of other drugs that produce perceptual abnormalities (3).

Several lines of evidence point to the rising popularity of recreational Salvia and SA use in the US (4–8). National Survey on Drug Use and Health (2006) data suggest that the rates of SA use among adolescents (.6%) and young adults (1.7%) are greater than that of other common hallucinogenic drugs such as lysergic acid diethylamide (LSD), ketamine, phencyclidine, and dimethyltryptamine (9). These rates of SA exposure increased from 1.5% in 2006 to 3.7% by 2010. Salvia products are readily available both locally and via the Internet. Salvia and SA are not federally regulated in the US, although the Drug Enforcement Agency has listed them as "drugs of concern," and 13 states have begun to regulate their use.

The human literature on SA effects is limited by a preponderance of anecdotal reports (1,5–7,9–11). Salvia produces a rapid onset of transient mood alterations, dissociative symptoms, and psychotomimetic effects. The anecdotal literature is difficult to interpret because of the use of variable doses and routes of administration; the use of other drugs before, with, or after SA use; variable set and setting; and a lack of characterization of the subject samples.

Experimental data with Salvia/SA in humans include one study that developed a method to detect SA in biological fluids after smoking Salvia (12) and four on the effects of SA (13–16). Seibert (15) described subjective effects of oral, sublingual, and inhaled Salvia and SA administration in an open-label, uncontrolled study in 20 subjects. Mendelson et al. (14) reported no effects and undetectable SA blood levels with SA administered sublingually at doses up to 4 mg in eight subjects. The lack of effects in this study was likely due to low bioavailability of sublingual SA. Johnson et al. (13) administered 16 doses of inhaled SA in a fixed-order, ascending-dose, placebo-controlled, single-blind study of four subjects. Subjects experienced a rapid onset of transient hallucinogenic effects without any physiological changes. Finally, Addy (16) studied 30 healthy subjects who self-administered 1017 μg of inhaled SA on dried Salvia leaves or placebo (unenhanced dried Salvia leaves) in a partially blinded manner (blinded only to the first dose) (16). The latter two studies, although demonstrating the hallucinatory effects of SA, were also limited in the lack of randomization or objective outcomes, the use of fixed ascending order of doses (13), and the use of Salvia leaves as the vehicle and control (16).

SA has been reported to produce behavioral effects, cognitive impairments, and prolactin elevations in animals. Other KOR ago-

nists have been reported to increase prolactin and cortisol levels in rodents (17,18) and humans (19) and to reduce resting electroencephalogram (EEG) power in rats (20). Resting EEG is potentially informative, because it is sensitive to drug-induced changes in consciousness (21–23) and is altered in psychosis (24,25). Finally, the pharmacokinetics of SA have not been studied in humans. SA is rapidly metabolized to Salvinorin B (SB), which is a much less potent KOR agonist (26). However, these outcomes have not been studied thus far in humans.

The behavioral, subjective, cognitive, endocrine, and psychophysiological effects of SA and its pharmacokinetic profile in humans were characterized in a controlled study to address the limitations and gaps in the existing literature.

Methods and Materials

This study was approved by the institutional review boards at Yale University and the Veterans Affairs Connecticut Healthcare System and the US Food and Drug Administration and was carried out in accordance with the Helsinki Declaration of 1975.

Study Design

This double blind, randomized, placebo controlled, counterbalanced, crossover, 3-day study was conducted at the Neurobiological Studies Unit (Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut).

Subjects. As detailed in Supplement 1, a rigorous screening was conducted to include medically and psychiatrically healthy subjects, between 18 and 55 years of age with previous exposure to Salvia. Because Salvia users characteristically use other drugs (27), subjects with exposure to other drugs were included so that the sample would be representative. History provided by subjects was corroborated with an outside informant nominated by the subject. Subjects were instructed to refrain from alcohol, illicit drugs, caffeine, and prescription drugs from a week before the first test day until study completion. Subjects were paid $200/test day for their participation.

General Procedure and Test Days. Subjects presented to the research unit, approximately 1 hour before the scheduled time of administration of drug, during which they underwent a urine toxicology exam and pregnancy test (in women), had an IV line placed, and underwent baseline ratings. In-study safety procedures were in place as described previously (28). Prospective safety assessments were performed the day after the first and last test days and 1 and 3 months after study completion.

Drugs. Subjects on each test day inhaled one of two doses of active SA or placebo (in an aluminum container) administered through a commercially available vaporizer (see Supplement 1 for details). The SA was obtained from the laboratory of Dr. Bruce M. Cohen, McLean Hospital, Belmont, Massachusetts, and stored in the research pharmacy at the Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut. On the morning of each test day, the SA dose was prepared in the designated container by the research pharmacists. Placebo consisted of the container devoid of any SA. Subjects and raters were blinded to the dose administered.

Outcome Measures. See Supplement 1 for greater detail.

Subjective and Behavioral Effects. Subjective feeling states such as "high," "anxious," "drowsy," "irritable," and "anxious" were measured with a self-reported visual analog scale (VAS). Psychotomimetic symptoms were measured with the Positive and Negative Syndrome Scale (PANSS) (29) and the Psychotomimetic States Inventory (PSI) (30). Perceptual alterations were measured with the Clinician Administered Dissociative Symptoms Scale (CADSS) (31) and the Hallucinogen Rating Scale (HRS) (32,33).

Cognitive Effects. Phonological processing, working memory, and attention were assessed with a simple cognitive battery comprising the Digits Forward and Backward and Letter Number Sequence tasks of the Wechsler Adult Intelligence Scale-Revised (34).

Neuroendocrine Effects. Plasma cortisol and prolactin were assayed at various time points before and after SA inhalation. Levels were analyzed in duplicate by the Yale Center for Clinical Investigation, Yale University, New Haven, Connecticut.

SA and SB Levels. Both SA and SB levels were analyzed by Dr. E. Thomas Everhart at the Drug Dependence Research Center (Langley Porter Psychiatric Institute, University of California) with a slightly modified liquid-chromatographic-atmospheric pressure chemical ionization-tandem mass spectrometric method (14) (see Supplement 1 for details). The limits of quantitation were .5 ng/mL for both SA and SB in plasma.

Psychophysiological Effects. Three minutes of resting state EEG was obtained as subjects sat still with their eyes closed immediately after SA inhalation.

Data Analysis

Initially, data were examined descriptively with means, SDs, and graphs. Each outcome was tested for normality with Kolmogorov-Smirnov test statistics and normal probability plots. All PANSS, PSI, HRS and cognitive battery outcomes were approximately normally distributed. These outcomes were analyzed with linear mixed models, which included SA dose (placebo, low [8 mg], and high [12 mg]) and time (pre- vs. postinhalation) as within-subjects explanatory factors and random subject effects. The best-fitting variance-covariance structure was chosen on the basis of information criteria. Significant interactions between dose and time were interpreted by appropriate post hoc tests. Similar models were used to compare physiological measures and serum SA and hormone (log) levels across time. All CADSS and VAS outcomes were highly skewed. Thus, these non-normal outcomes were analyzed with the non-parametric approach for repeated measures data, in which data are ranked and then fitted with a mixed-effects model with an unstructured variance-covariance matrix and p values are adjusted for analysis of variance-type statistics (ATS) (35). In these models, SA (placebo, low dose, high dose, and time [pre- vs. posttreatment]) were included as within-subjects explanatory factors. The EEG power frequencies were compared with linear mixed models with dose and electrode (Cz, Pz, Oz) as within-subjects factors. All data were analyzed with SAS (version 9.2; SAS, Cary, North Carolina).

Results

Subjects were young (23.8 $\pm$ 3.2 years), predominantly male (90%), with 15.3 ($\pm$ 1.2) years of education, intelligence quotient scores of 117.2 ($\pm$ 7.1), and low (2.8 $\pm$ 2.8) psychosis proneness scores on the Schizotypal Personality Questionnaire (Table S2 in Supplement 1). Nine subjects completed all 3 test days, and one dropped out after his second test day. All 10 subjects were included in the analyses. None of the subjects met criteria for alcohol or substance dependence. All subjects had previous exposure to SA and other illicit substances (Table S3 in Supplement 1). For parsimony, only positive results are reported in detail here.

Subjective Reports

The following are quotations from subjects describing SA-induced changes:

Somaesthetic changes: "I felt a cold prickling feeling on my legs," "...tingling in my fingers," "...felt a pattern sweep over me like a wave...I felt as well as saw the waves..."

Feelings of dissociation: "I felt like I was on a different planet…"

Feelings of detachment: "I could see you and hear you, but I felt separated and distant from you…"

Heightened awareness of visual and/or auditory stimuli: "the patterns on the curtain appeared more prominent…the contrast was more vivid," "the air-conditioner seemed louder…"

Withdrawal into self: "… I wished I didn't have to answer questions…," "…wished I was left alone…"

Changes in concentration/increased distractibility: "…felt distracted by background sounds," "I felt mesmerized by the pattern on the door"

Increased intrusive thoughts (interfering with ability to concentrate): "…lot of thoughts about my day…"

Changes in mood: "calmer," "more comfortable"

Subjective Effects—VAS

There was a main effect of SA administration on feeling "drowsy" [ATS(1.91) = 4.55, $p = .01$] such that both low [ATS(1) = 4.9, $p = .03$] and high [ATS(1) = 3.99, $p < .05$] doses of SA produced less drowsiness compared with placebo. The SA administration did not pro-
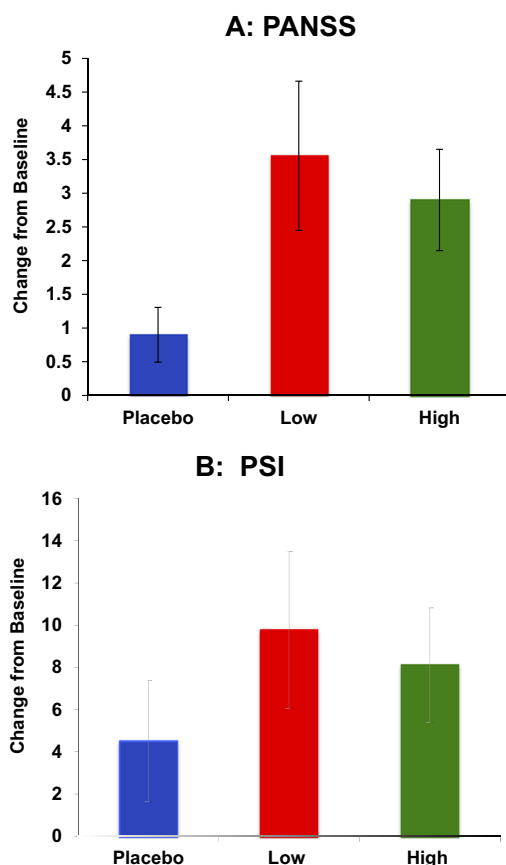
Figure 1. Salvinorin A (SA) administration produced transient psychotomimetic effects measured as increases on Positive and Negative Syndrome Scale (PANSS) positive subscale **(A)** and the Psychotomimetic States Inventory (PSI) **(B)**. Blue: placebo; red: SA Low Dose (8 mg); green: SA High Dose (12 mg). The SA doses are depicted as bars along the x-axis. Change in PANSS **(A)** and PSI scores **(B)** are on the y-axis. Error bars represent SEM.
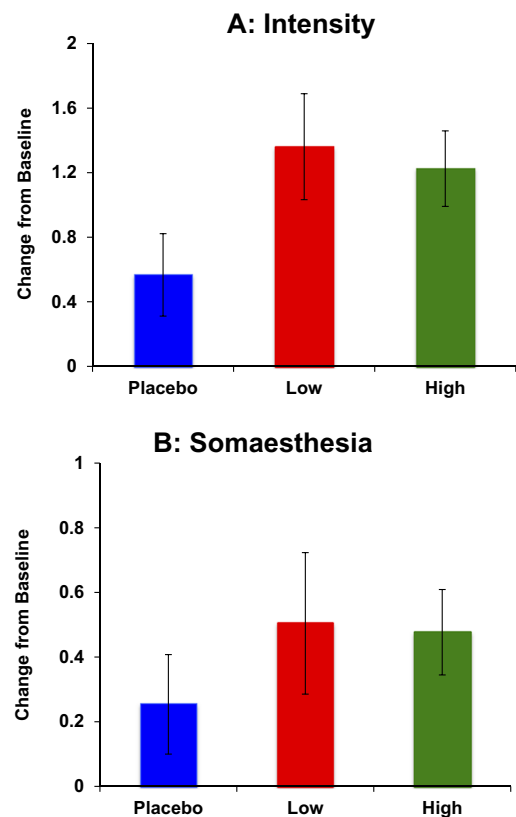
Figure 2. Salvinorin A (SA) administration produced transient perceptual alterations measured as increases on the Hallucinogen Rating Scale (HRS) "Intensity" **(A)** and "Somaesthesia" **(B)** subscales. The SA doses: placebo (blue), low (8 mg) (red), and high (12 mg) (green) are depicted as bars along the x-axis. Change in HRS scores is on the y-axis. Error bars represent SEM.

duce any changes on the VAS for feeling "high," "calm," "sad," "irritable," or "anxious."

Psychotomimetic Effects

PANSS. SA produced increases in psychotomimetic effects as measured by the PANSS Positive scores (Figure 1A). The dose × time interaction was significant [$F(2,43) = 3.12, p = .05$]. Post hoc analyses revealed that low-dose SA increased positive symptoms significantly, relative to placebo [$F(1,43) = 4.62, p = .04$], whereas these increases trended toward significance for the high dose [$F(1,43) = 3.37, p = .07$]. SA produced an increase in PANSS General Psychopathology scores: the dose × time interaction was significant [$F(2,43) = 3.52, p = .04$], driven by an increase in general symptoms for low dose SA [$F(1,43) = 4.65, p = .04$]. Finally, SA also produced an increase in PANSS total scores: the dose × time interaction trended toward significance [$F(2,43) = 2.83, p = .07$]. Post hoc analyses revealed that this effect was driven by increases due to low-dose SA [$F(1,43) = 4.1, p < .05$].

PSI. The PSI, which also measured SA-induced psychotomimetic effects, showed a dose × time interaction [$F(2,43) = 3.11, p = .05$] driven by increases on PSI scores due to both low- [$F(1,43) = 8.01, p < .01$] and high-dose SA [$F(1,43) = 10.29, p < .01$] (Figure 1B).

Perceptual Alterations

HRS. SA administration induced perceptual alterations measured by the HRS subscales for Intensity, Somaesthesia, and Perception (Figure 2). On the "Intensity" subscale (Figure 2A), there was a
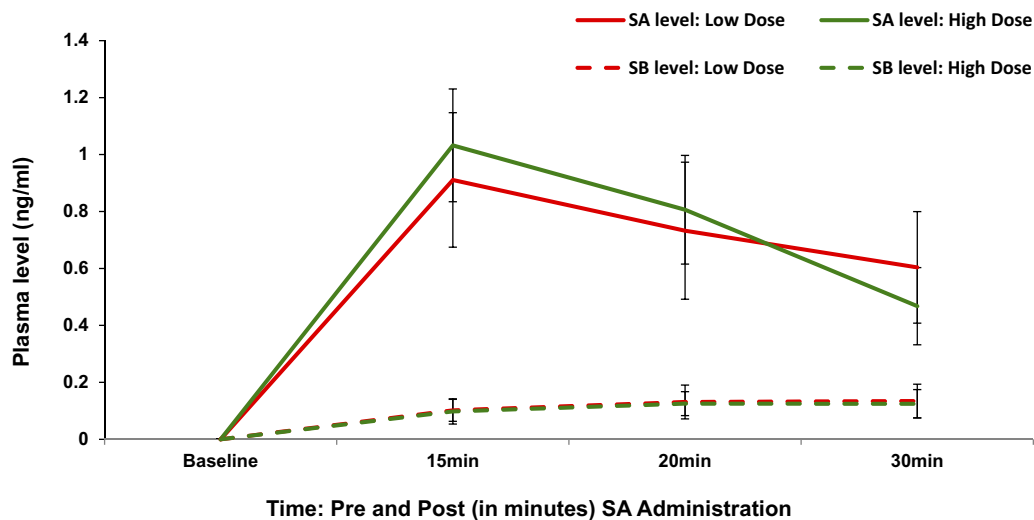
Figure 3. Salvinorin A (SA) produced increases in plasma levels of SA and Salvinorin B (SB) measured in a subsample of subjects ($n = 7$). Neither SA nor SB levels were detectable before drug administration (baseline). Time is on the x-axis as baseline (Pre) and 15, 20, and 30 min after SA administration. Plasma levels of SA and SB are on the y-axis. Separate lines depict the low and high dose of SA. Error bars represent SEM. Red: SA low dose (8 mg); green: SA high dose (12 mg).

main effect of dose [ATS(1.45) = 3.71, p = .04], driven by increases in scores due to the low dose [ATS(1) = 4.24, p = .04]. On the "Somaesthesia" subscale (Figure 2B) there was a main effect of dose [ATS(1.9) = 4.11, p = .02], primarily driven by increases due to the low dose [ATS(1) = 11.4, p < .001]. There was also a main effect of dose on "Perception" [ATS(1.65) = 3.35, p = .04], again driven by increases due to low dose [ATS(1) = 4.13, p = .04].

CADSS. SA administration did not produce any significant changes on the CADSS patient-rated [ATS(1.73) = .96, p = .37] or clinician-rated subscales [ATS(1.36) = .73, p = .43].

Cognitive Battery

SA administration did not produce any effects on performance on the Digit Forward [F(2,9) = .4, p = .68], Digit Backward [F(2,17) = .33, p = .73], or Letter Number Sequencing tasks [F(2,17) = .54, p = .59].

Plasma SA and SB Levels

Only samples from active dose conditions were analyzed for SA and SB levels (Figure 3); the main comparison was between blood levels before and after drug administration. Both doses of SA produced a rapid increase in SA levels compared with pre-administration levels [F(3,38) = 29.4, p < .0001] but without significant differences between the two active doses. The levels of SA peaked at + 15 min after administration.

Both doses of SA also produced an increase in SB levels compared with pre-administration levels [F(3,38) = 8.66, p = .0002].

Neuroendocrine Effects

Cortisol Levels. Low-dose SA significantly elevated plasma cortisol levels [F(2,120) = 3.11, p < .05], which returned to baseline 60 min after SA inhalation [F(4,120) = 18.69, p < .0001] (Figure 4A).

Prolactin Levels. Both doses of SA significantly elevated plasma prolactin levels [F(8,120) = 4.07, p = .0003], which also returned to baseline by 60 min after administration (Figure 4B).

Physiological Effects

Neither dose of SA produced any significant changes in heart rate or systolic or diastolic blood pressure in any subject.

Resting State Electroencephalography

SA administration decreased resting state EEG spectral power across all frequencies examined (although not all frequency bands reached significance) (Figure 5). Compared with placebo, SA was associated with lower β power at both doses [F(68,2) = 5.47, p < .006]. The SA also lowered θ power with a trend toward significance [F(68,2) = 2.44, p = .09]. The effects of SA on δ, α, and γ frequencies were not statistically significant.

Safety

No serious adverse events (death, hospital stay, or emergency room visit) occurred during or after the study. One subject dropped out for unspecified reasons, after reporting no effects on either of the test days in which he participated. No test days were terminated prematurely nor were rescue medications necessary. Exit interviews conducted in a subsample of subjects revealed that subjects felt they had been adequately informed about the risks of the study. Follow-up assessments at 1 and 3 months revealed no new psychiatric symptoms or increased Salvia consumption.

Discussion

This is the first report to our knowledge on a wide range of dose-related subjective, behavioral, cognitive, cardiovascular, psychophysiological, and neuroendocrine effects and safety of inhaled SA in a randomized, double-blind, placebo-controlled, crossover, counterbalanced study in healthy humans.

Onset and Duration of Effects

As expected, SA produced very short-lasting psychoactive effects with some psychotomimetic features, most notably somaesthetic changes, dissociative effects, and perceptual alterations. Consistent with anecdotal data and experimental reports (13,16), the onset of SA effects was very rapid (within seconds to minutes) as captured on the HRS "Intensity" subscale, with a peak within 10 min and a return to baseline within 30 min. No subjects reported any lingering effects at the time of discharge (90 min after inhalation) or any persistent or recurrent effects during the safety follow-ups.

A: Plasma Cortisol

B: Plasma Prolactin

— Placebo   — Low   — High
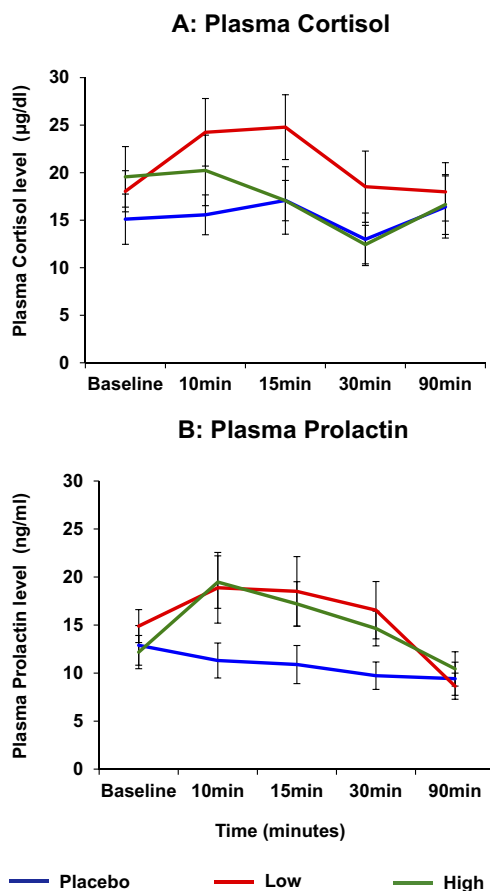
Figure 4. Salvinorin A (SA) administration produced elevations in plasma cortisol **(A)** and prolactin **(B)**. Time is on the x-axis as baseline (Pre) and 10, 15, 30, and 90 min after SA administration. Plasma cortisol (μg/dL) and prolactin (ng/mL) levels are on the y-axis. Separate lines depict the doses of SA. Error bars represent SEM.

Magnitude of Effects

The magnitude of psychotomimetic effects induced by SA as measured by the PANSS positive subscale (3.5-point increase) and PSI (10-point increase) was comparable to the effects of δ-9-tetra-hydrocannabinol and ketamine on those measures (28,30,36).

Comparison of SA Administration in This Study to Recreational Use by Subjects

Peak effects in this study were rated as only 20%–30% of the peak effects experienced with recreational SA use. A number of factors might account for the differences, the most obvious being that the drug was delivered in this study more slowly and at lower doses than characteristic of recreational use. Although a vaporizer reaches the target temperature within minutes, the typical recreational method of delivery (in which subjects apply direct heat to a glass pipe or aluminum foil containing Salvia) attains this temperature instantaneously. This factor should also be taken into consideration while comparing these data with other studies of inhaled SA (13,16). Secondly, in this study subjects received pure SA, whereas with recreational use either salvia leaves or extract-enhanced leaves are used. The contribution of other psychoactive compounds present in these preparations might alter subjective effects. Finally, the combination of variable strength of Salvia products and variability in the amount used recreationally makes accurate estimation of recreational dose near impossible. This limits the ability

to accurately compare the doses in this study with recreational doses. These considerations notwithstanding, subjects were asked to compare effects in this laboratory study with those associated with recreational use to infer how doses used in this study compared with doses used recreationally.

Endocrine Effects of SA

Elevations in serum prolactin are a well-recognized biomarker of KOR agonism in rodent and nonhuman primates (37–39). This study is the first to demonstrate endocrine effects of SA in humans and thus provides clear objective evidence of the centrally mediated effects of SA. The KORs are abundantly distributed in the hypothalamus (40,41), and KOR agonists are known to increase prolactin levels, but the exact mechanism remains unclear. One possibility is that SA via KOR agonism might lower dopamine (DA) levels in the tuberoinfundibular pathway, similar to the effects of KOR agonism on DA in other brain regions (42–44).

This is the first report to our knowledge on the cortisol elevating effects of SA in humans; this effect is consistent with the cortisol elevating effects of other KOR agonists observed in animals and humans (17,19). The cortisol stimulatory effect in nonhuman primates was shown to be specific to KOR agonism and not produced by μ or δ opioid agonists and was blocked by a selective KOR antagonist (17). Collectively, the results of the current study and previous studies demonstrate that, similar to other KOR agonists, SA stimulates the hypothalamic-pituitary-axis activity in humans.

Psychophysiological (EEG) Effects

No previous study has examined the psychophysiological effects of SA in humans. Although all doses of SA decreased broadband resting-state EEG spectral power, the reductions were significant in the β-band (13–29 Hz) and trended toward significance in the θ band (4–7 Hz). These effects are consistent with a previous human study showing that the KOR agonist pentazocine decreased resting EEG power in the θ, α, and β frequency bands (45). However, the pattern of SA effects on resting EEG are different from that of
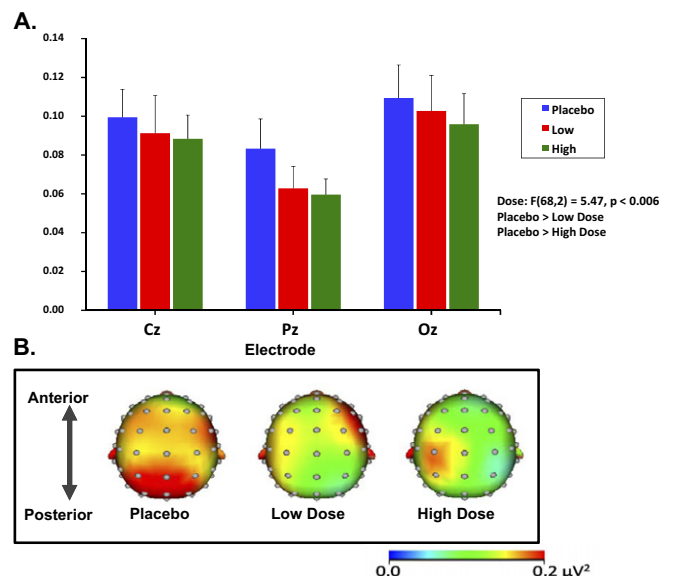
Figure 5. Salvinorin A (SA) administration induced reductions in resting β-band electroencephalogram power. **(A)** Grand-averaged resting electroencephalogram spectral power in the β range (13–29 Hz) at midline electrode sites. Error bars represent SEM. **(B)** Topographic maps indicating grand-averaged β power across the placebo and the two active SA doses.

other hallucinogens such as mescaline, ketamine, and ayahuasca (46–48), which are associated with increases or no change in β power. These differences serve to highlight that SA produces its effects via a unique mechanism and thus might have a distinct psychophysiological profile. Although the neurochemical mechanisms of these changes as well as their functional implications remain unclear, the current findings suggest that resting EEG might provide an objective, behaviorally independent index of KOR agonist effects on brain function.

Thus the inclusion of outcomes such as resting EEG, hormonal levels, and SA and SB levels in this study provide objective biological correlates of SA effects in humans. The method of delivery, doses of SA, and overall study design are validated by effects detected on subjective as well as objective outcomes. This is particularly crucial, given the wide variability in subjective effects that might be reported in such a study.

Relevance to Abuse

Salvinorin A is now recognized as a potential drug of abuse with increasing use especially among youth. However, several lines of evidence suggest that, in contrast to other drugs of abuse with addictive liability, SA is less likely to be used compulsively, repetitively, or persistently. In this study SA did not produce euphoria, an effect that is common to most addictive drugs. Furthermore, the findings from surveys of SA users (5) and reports from our subjects suggest that recreational Salvia use is sporadic, in contrast to the compulsive, repetitive use and persistent use pattern of addictive drugs.

Addictive drugs share in common the capacity to increase DA in the nucleus accumbens. The SA and synthetic κ opioid agonists (U-69593, U-50488, and R-84760) decrease DA levels in the nucleus accumbens of rodents (43,49–52). Synthetic KOR agonists and SA induce conditioned place aversion (53–57). The KOR agonists reduce cocaine self-administration (58–61), cocaine-induced hyperlocomotion (57,62–64), cocaine-induced reinstatement of drug self-administration (61,65–67), and cocaine-induced behavioral sensitization (62,68–71). However, one study did show intracerebroventricular SA self-administration and conditioned place preference in mice at relatively low doses (72). The KOR agonists also reduce intracranial self-stimulation (73) consistent with a profile of aversive effects.

Collectively the evidence suggests that SA and other KOR agonists are likely to have low addiction liability. In fact, KOR agonists have been studied as potential treatment for addictions (74–78), but further development has been hampered by adverse effects (73,77,79–84). Most likely, SA is used for its perceptual altering effects. Because the concept of drug "abuse" includes "use for nontherapeutic effects," SA might be considered an agent with recreational abuse liability similar to LSD. The intensity of SA effects reported by recreational users is highly variable, ranging from mild perceptual alterations to frank psychosis prompting contact with poison control or necessitating emergency care and hospital stay (85,86). In the current study too, the intensity of SA effects showed significant inter-individual variability. Finally, in individuals who might be vulnerable to psychotic illnesses or with an established psychotic disorder, SA exposure might have particularly devastating consequences.

Relevance to Psychosis

The results of this study are also relevant to understanding the pathophysiology of psychosis and to drug development. According to the dominant DA hypothesis, increased mesolimbic DA is implicated in the pathophysiology of the positive symptoms of psycho-

sis (87). Salvinorin A induces psychosis-like effects but decreases DA in several brain regions (43,44), which arguably was indirectly reflected in the increased prolactin levels observed in this study. Furthermore, the DA D2 receptor antagonist haloperidol does not attenuate the deficits in prepulse inhibition produced by KOR activation (88). The only known mechanism of action of SA is KOR agonism. It does not have affinity for serotonin (5-HT2), DA, cannabinoid (CB1R), or NMDA receptor systems that have been implicated in the mechanism of other drugs that produce psychotomimetic effects (3). Therefore, KOR agonism might be relevant to the pathophysiology of psychosis, and the study of the KOR system with a probe such as SA might shed more light on the involvement of this system in the pathophysiology of psychosis. Further studies are necessary to investigate the precise mechanism(s) underlying the psychotomimetic effects of SA. Finally, although admittedly simplistic and speculative, the association between KOR agonism and psychosis raises the possibility that KOR antagonists might have antipsychotic potential.

Strengths and Limitations

Important strengths of this study include the double-blind, randomized, placebo-controlled, crossover design; the use of multiple doses; the estimation of blood levels; and the use of a range of objective and subjective measures. Although the standardized set, setting, and validation of method of delivery with objective measures and blood levels are strengths of this experimental approach, they limit generalizability of these findings to recreational use. Finally, the lack of differences in both plasma levels and responses between the two doses did not permit characterization of the dose-response profile of SA.

Future Directions

Future studies should focus on characterizing the safety, tolerability, and effects of a wider dose range of SA in humans. Furthermore, although preclinical data suggest that SA acts solely via the KOR, whether this is indeed the case in humans is unclear. Studies examining the effects of KOR blockade on the effects of SA and receptor-imaging studies will help answer these questions.

Supplementary material cited in this article is available online.

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